

We Claim:

5 1. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period.

2. A material according to claim 1 wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 1 day to greater than 500 days.

3. A material according to claim 1 wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 5 days to about 30 days.

4. A material according to claim 1 wherein the degradation control region comprises at least one selectable hydrolytically degradable moiety.

5 5. A material according to claim 4 wherein the hydrolytically degradable moiety includes saturated di-acids, unsaturated di-acids, poly(glycolic acid), poly(DL-lactic acid), poly(L-lactic acid), poly( $\xi$ -caprolactone), poly( $\delta$ -valerolactone), poly( $\gamma$ -butyrolactone), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(orthocarbonates), or poly(phosphoesters).

6. A material according to claim 1 wherein the degradation control region comprises at least one selectable enzymatically degradable moiety.

7. A material according to claim 6 wherein the enzymatically degradable moiety includes Leu-Glyc-Pro-Ala (collagenes sensitive linkage)

sub

A2

or Gly-Pro-Lys (plasmin sensitive linkage).

- 5 8. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link over time to form a non-liquid, three-dimensional network, the polymer including a cross-linking group selected to achieve a desired cross-linking period.

9. A material according to claim 8 wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to greater than 10 hours.

10. A material according to claim 8 wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to about 10 minutes.

11. A material according to claim 8 wherein the cross-linking group is selected to achieve a desired cross-linking period within a range from less than 1 second to about 2 minutes.

12. A material according to claim 8 wherein the cross-linking group is selected to react with at least one thiol.

13. A material according to claim 8 wherein the cross-linking group is selected from a group consisting essentially of vinyl sulfone, N-ethyl maleimide, iodoacetamide, and orthopyridyl disulfide.

14. A material according to claim 8 wherein the cross-linking group is selected to react with at least one amine.

15. A material according to claim 8 wherein the cross-linking group is selected from a group consisting essentially of aldehydes.

16. A material according to claim 8

5 wherein the cross-linking group is selected from a group consisting essentially of active esters, epoxides, oxycarbonylimidazole, nitrophenyl carbonates, tresylate, mesylate, tosylate, and isocyanate.

17. A material according to claim 8 wherein the cross-linking group includes an ester of N-hydroxysuccinimide.

18. A material according to claim 8 wherein the protein solution includes a buffer.

19. A material according to claim 18 wherein the buffer includes carbonate or phosphate.

5 20. A material according to claim 1 or 8 wherein the polymer comprises a compound of the formula  $\text{PEG}-(\text{DCR}-\text{CG})_n$ , where PEG is poly(ethylene glycol), DCR is the degradation control region, CG is the cross-linking group, and n is equal to or greater than three.

21. A material according to claim 20 wherein the compound comprises a multi-armed polymer structure.

22. A material according to claim 1 or 8 wherein the protein solution comprises at least one non-immunogenic, hydrophilic protein.

5 23. A material according to claim 22 wherein the non-immunogenic, hydrophilic protein is selected from a group consisting essentially of serum, serum fractions, and solutions of albumin, gelatin, antibodies, fibrinogen, and serum proteins.

24. A material according to claim 1 or 8 wherein the protein solution comprises at least one water soluble derivative of a hydrophobic protein.

25. A material according to claim 24 wherein the water soluble derivative of a hydrophobic protein is selected from a group consisting essentially of comprising solutions of collagen, elastin,

5 chitosan, and hyaluronic acid.

26. A material according to claim 1 or 8 wherein the protein solution comprises at least one hybrid protein.

27. A material according to claim 1 or 8 wherein the protein solution comprises at least one synthetic amino acid sequence.

28. A material according to claim 1 or 8 wherein the protein solution comprises recombinant or natural human serum albumin.

29. A material according to claim 28 wherein the human serum albumin is at a concentration of about 25% or less.

5 30. A material according to claim 1 or 8 wherein the polymer solution includes a derivative of a polymer selected from a group consisting essentially of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene glycol)-co-poly(propylene glycol) block copolymers, or electrophilically derivatized polysaccharides, carbohydrates, or proteins.

31. A material according to claim 1 or 8 wherein the polymer solution comprises at least one hybrid protein.

32. A material according to claim 1 or 8 wherein the polymer solution comprises at least one synthetic amino acid sequence.

33. A material according to claim 1 or 8 wherein the polymer is comprised of poly(ethylene glycol) (PEG).

34. A material according to claim 33 wherein the PEG has a molecular weight of between about 1,000 and about 30,000 g/mole.

35. A material according to claim 33

wherein the PEG has a molecular weight of between about 2,000 and about 15,000 g/mole.

36. A material according to claim 33

wherein the PEG has a molecular weight of between about 10,000 and 15,000 g/mole.

37. A material according to claim 33

wherein the PEG comprises a multi-armed polymer structure.

38. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link over time to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period.

39. A material according to claim 38

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 1 day to greater than 500 days.

40. A material according to claim 38

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 5 days to about 30 days.

41. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to greater than 10 hours.

42. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to about 10 minutes.

43. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range from less than 1 second to about 2 minutes.

44. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

10 instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal a vascular puncture site.

45. A system according to claim 44

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

46. A system according to claim 44 or 45

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of about 15 to 60 seconds.

47. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a

10 liquid form, the polymer including a degradation control  
region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

15 instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
mixture to seal tissue from blood leaks.

48. A system according to claim 47

wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
30 days.

49. A system according to claim 47 or 48

wherein the cross-linking group is selected to  
achieve a desired cross-linking period of less than one  
second.

50. A system for forming a biocompatible material  
comprising

a protein solution,

5 a polymer solution including a derivative of a  
hydrophilic polymer with a functionality of at least  
three, wherein, upon mixing, the protein solution and the  
polymer solution cross-link to form a non-liquid, three-  
dimensional network that degrades over time back to a  
liquid form, the polymer including a degradation control  
10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

15 instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
mixture to seal tissue from gas leaks.

51. A system according to claim 50

wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
30 days.

52. A system according to claim 50 or 51

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

53. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

10 instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal tissue from liquid leaks.

15 54. A system according to claim 53

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

55. A system according to claim 53 or 54

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

56. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control



10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
15 mixture to seal tissue from solid leaks.

57. A system according to claim 56

wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
30 days.

58. A system according to claim 56 or 57

wherein the cross-linking group is selected to  
achieve a desired cross-linking period of less than one  
second.

~~59. A system for forming a biocompatible material  
comprising~~

a protein solution,

5 a polymer solution including a derivative of a  
hydrophilic polymer with a functionality of at least  
three, wherein, upon mixing, the protein solution and the  
polymer solution cross-link to form a non-liquid, three-  
dimensional network that degrades over time back to a  
liquid form, the polymer including a degradation control  
10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
15 mixture to prevent post-operative adhesions.

60. A system according to claim 59

wherein the degradation control region is selected  
to achieve a desired degradation period within a range of  
approximately 5 to 30 days.

61. A system according to claim 59 or 60

wherein the cross-linking group is selected to

achieve a desired cross-linking period of less than one second.

62. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

10 instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to repair a tissue void.

63. A system according to claim 62

wherein the degradation control region is selected to achieve a desired degradation period in a range of approximately 30 to 60 days.

64. A system according to claim 62 or 63

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 5 seconds.

65. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period,

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the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to augment tissue.

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66. A system according to claim 65

wherein the degradation control region is selected to achieve a desired degradation period of approximately one year.

67. A system according to claim 65 or 66

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 120 seconds.

68. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

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instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to embolize an arterio-venous malformation.

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69. A system according to claim 68

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 30 to 120 seconds.

70. A system for forming a biocompatible material comprising

a protein solution,

5 a polymer solution including a derivative of a  
hydrophilic polymer with a functionality of at least  
three, wherein, upon mixing, the protein solution and the  
polymer solution cross-link to form a non-liquid, three-  
dimensional network that degrades over time back to a  
liquid form, the polymer including a degradation control  
10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
mixture to fill an aneurysm.  
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71. A system according to claim 70

wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
one year.

72. A system according to claim 70 or 71

wherein the cross-linking group is selected to  
achieve a desired cross-linking period of approximately  
5 to 30 seconds.

~~73.~~ A system for forming a biocompatible material  
comprising

a protein solution,

5 a polymer solution including a derivative of a  
hydrophilic polymer with a functionality of at least  
three, wherein, upon mixing, the protein solution and the  
polymer solution cross-link to form a non-liquid, three-  
dimensional network that degrades over time back to a  
liquid form, the polymer including a degradation control  
10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
mixture to deliver a pharmaceutical.  
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74. A system according to claim 73  
wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
one year.

75. A system according to claim 73 or 74  
wherein the cross-linking group is selected to  
achieve a desired cross-linking period of approximately  
5 to 30 seconds.

76. A system for forming a biocompatible material  
comprising

a protein solution,

5 a polymer solution including a derivative of a  
hydrophilic polymer with a functionality of at least  
three, wherein, upon mixing, the protein solution and the  
polymer solution cross-link to form a non-liquid, three-  
dimensional network that degrades over time back to a  
liquid form, the polymer including a degradation control  
10 region selected to achieve a desired degradation period,  
the polymer also including a cross-linking group selected  
to achieve a desired cross-linking period, and

15 instructions for forming a mixture of the protein  
solution and polymer solution and for applying the  
mixture to deliver cells.

77. A system according to claim 76  
wherein the degradation control region is selected  
to achieve a desired degradation period of approximately  
1 week to 6 months.

78. A system according to claim 76 or 77  
wherein the cross-linking group is selected to  
achieve a desired cross-linking period of approximately  
5 to 30 seconds.

79. A system according to claim 44 or 47 or 50 or  
53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the degradation control region comprises at  
least one selectable hydrolytically degradable moiety.

80. A system according to claim 79  
wherein the hydrolytically degradable moiety includes saturated di-acids, unsaturated di-acids, poly(glycolic acid), poly(DL-lactic acid), poly(L-lactic acid), poly( $\xi$ -caprolactone), poly( $\delta$ -valerolactone), poly( $\gamma$ -butyrolactone), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(orthocarbonates), or poly(phosphoesters).

81. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the degradation control region comprises at least one selectable enzymatically degradable moiety.

82. A system according to claim 81

wherein the enzymatically degradable moiety includes Leu-Glyc-Pro-Ala (collagenes sensitive linkage) or Gly-Pro-Lys (plasmin sensitive linkage).

83. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected to react with at least one thiol.

84. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected from a group consisting essentially of vinyl sulfone, N-ethyl maleimide, iodoacetamide, and orthopyridyl disulfide.

85. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected to react with at least one amine.

86. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected from a group consisting essentially of aldehydes.

87. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

5 wherein the cross-linking group is selected from a group consisting essentially of active esters, epoxides, oxycarbonylimidazole, nitrophenyl carbonates, tresylate, mesylate, tosylate, and isocyanate.

88. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group includes an ester of N-hydroxysuccinimide.

89. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution includes a buffer.

90. A system according to claim 89

wherein the buffer includes carbonate or phosphate.

91. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

5 wherein the polymer comprises a compound of the formula  $\text{PEG}-(\text{DCR}-\text{CG})_n$ , where PEG is poly(ethylene glycol), DCR is the degradation control region, CG is the cross-linking group, and n is equal to or greater than three.

92. A system according to claim 91

wherein the compound comprises a multi-armed polymer structure.

93. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one non-immunogenic, hydrophilic protein.

94. A system according to claim 93

5 wherein the non-immunogenic, hydrophilic protein is selected from a group consisting essentially of serum, serum fractions, and solutions of albumin, gelatin, antibodies, fibrinogen, and serum proteins.

95. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one

water soluble derivative of a hydrophobic protein.

96. A system according to claim 95

wherein the water soluble derivative of a hydrophobic protein is selected from a group consisting essentially of comprising solutions of collagen, elastin, chitosan, and hyaluronic acid.

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97. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one hybrid protein.

98. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one synthetic amino acid sequence.

99. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises recombinant or natural human serum albumin.

100. A system according to claim 99

wherein the human serum albumin is at a concentration of about 25% or less.

101. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution includes a derivative of a polymer selected from a group consisting essentially of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethylloxazoline), poly(ethylene glycol)-co-poly(propylene glycol) block copolymers, or electrophilically derivatized polysaccharides, carbohydrates, or proteins.

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102. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution comprises at least one hybrid protein.



103. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution comprises at least one synthetic amino acid sequence.

104. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer is comprised of poly(ethylene glycol) (PEG).

105. A system according to claim 104

wherein the PEG has a molecular weight of between about 1,000 and about 30,000 g/mole.

106. A system according to claim 104

wherein the PEG has a molecular weight of between about 2,000 and about 15,000 g/mole.

107. A system according to claim 104

wherein the PEG has a molecular weight of between about 10,000 and 15,000 g/mole.

108. A system according to claim 104

wherein the PEG comprises a multi-armed polymer structure.

109. A biocompatible material comprising a mixture of a protein solution and a polymer solution which, upon mixing, cross-link to form a non-liquid, three-dimensional network, and an agent that undergoes color change in response to cross-linking of the mixture.

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110. A material according to claim 109

wherein the agent undergoes color change in response to change in pH.

111. A material according to claim 109

wherein the agent exhibits a first color when the mixture is in a liquid state and a second color, different than the first color, when the mixture forms the non-liquid, three-dimensional network.

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112. A material according to claim 109

wherein the agent exhibits a first color when the

5 mixture is in transition between a liquid state and the non-liquid, three dimensional network, and a second color, different than the first color, when the mixture forms the non-liquid, three-dimensional network.

113. A material according to claim 109 wherein the agent includes xylenol blue.

114. A material according to claim 109 wherein the agent includes phenol red.

115. A material according to claim 109 wherein the agent includes a mixture of xylenol blue and phenol red.

116. A material according to claim 109 wherein the agent includes phenolphthalein.

117. A material according to claim 109 wherein the agent includes o-cresolphthalein.

118. A material according to claim 109 wherein the agent includes bromothymol blue.

119. A material according to claim 109 wherein the agent includes a mixture of bromothymol blue and phenolphthalein or o-cresolphthalein.